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β_2-Microglobulin Concentration in Plasma and Production in Liver Cirrhosis

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Summary: The β_2-microglobulin plasma level is often high in patients suffering from cirrhosis. Many authors believe this to be due to an increased production, provided that the creatinine level is in the normal range. In the present study, alterations in the plasma level and production of β_2-microglobulin were investigated in patients with liver cirrhosis without overt renal failure.

62 patients, 48 men and 14 women, suffering from liver cirrhosis were examined. The glomerular filtration rate (GFR) and plasma β_2-microglobulin were measured in all patients and in 16 controls. As β_2-microglobulin is freely filtered by glomeruli and its extrarenal catabolism is negligible, the β_2-microglobulin filtration rate was calculated as the product of the β_2-microglobulin plasma level times the GFR. In steady state conditions, the β_2-microglobulin filtration rate may be used as an indirect index of β_2-microglobulin production.

The β_2-microglobulin plasma level was high in 26 patients; however, only 12 of them showed a definite rise in β_2-microglobulin production, as shown by an increased β_2-microglobulin filtration rate. The 14 patients with high β_2-microglobulin plasma levels without high β_2-microglobulin filtration rates obviously showed a decreased GFR; however, creatinine was not increased because of its small sensitivity as an index of renal function.

A linear correlation was found between IgG and the β_2-microglobulin filtration rate ($r = 0.52$; $p < 0.02$), not between IgG and the β_2-microglobulin plasma level. The other indices of liver damage were not related to the β_2-microglobulin filtration rate or plasma level.

In conclusion:

1) About half of the patients with high β_2-microglobulin plasma levels and normal creatinine actually showed an increased β_2-microglobulin production evaluated by the β_2-microglobulin filtration rate. In the others the high β_2-microglobulin plasma level was due to a subtle renal impairment which occurred before an increase in serum creatinine. Therefore, the β_2-microglobulin plasma level was not a reliable index of β_2-microglobulin production.

2) The use of the β_2-microglobulin filtration rate as an index of β_2-microglobulin production allowed us to detect a relationship between β_2-microglobulin production and immunological alterations (IgG level) in cirrhosis.

Konzentration von β_2-Mikroglobulin im Plasma und Bildung bei Lebercirrhose

Zusammenfassung: Bei Patienten mit Lebercirrhose ist die Konzentration von β_2-Mikroglobulin im Plasma oft hoch. Viele Autoren glauben, dies beruhe auf einer gesteigerten Bildung, vorausgesetzt, die Kreatininkonzentration ist im Normbereich. In der vorliegenden Arbeit untersuchten wir Änderungen in der Konzentration von β_2-Mikroglobulin und seiner Bildung bei Patienten mit Lebercirrhose ohne offenbares Nierenversagen.

62 Patienten, 48 Männer und 14 Frauen mit Lebercirrhose wurden untersucht. Glomeruläre Filtrationsrate und β_2-Mikroglobulin wurden bei allen Patienten und 16 Gesunden bestimmt. Da β_2-Mikroglobulin glomerulär frei filtriert wird und sein extrarenaler Stoffwechsel vernachlässigbar ist, wurde die Filtrationsrate für β_2-Mikroglobulin als Produkt von Konzentration im Plasma und glomerulärer Filtrationsrate berechnet. Unter Gleichgewichtsbedingungen kann die Filtrationsrate für β_2-Mikroglobulin als indirektes Maß für seine Bildung angesehen werden.

Die Konzentration von β_2-Mikroglobulin im Plasma von 26 Patienten war hoch, jedoch nur 12 von ihnen zeigten einen deutlichen Anstieg der Bildung von β_2-Mikroglobulin, wie die gesteigerte Filtrationsrate zeigt. Die 14 Patienten mit hoher Konzentration von β_2-Mikroglobulin im Plasma ohne hohe Filtrationsraten für β_2-Mikroglobulin zeigten deutlich eine verringerte glomeruläre Filtrationsrate; Kreatinin als Indikator der Nierenfunktion war jedoch nicht erhöht, weil es nur eine geringe Sensitivität hierfür aufweist.

Eine lineare Korrelation bestand zwischen IgG und Filtrationsrate von β_2-Mikroglobulin ($r = 0{,}52$; $p < 0{,}02$), nicht zwischen IgG und Konzentration von β_2-Mikroglobulin im Plasma. Andere Indikatoren für Leberschäden zeigten keine Beziehung zur Filtrationsrate von β_2-Mikroglobulin oder seiner Konzentration im Plasma.

Schlußfolgerungen:

1. Etwa die Hälfte der Patienten mit hoher Konzentration von β_2-Mikroglobulin im Plasma und normalem Kreatinin zeigte eine erhöhte β_2-Mikroglobulinbildung, bestimmt aus der β_2-Mikroglobulin-Filtrationsrate. Bei den anderen war die hohe Konzentration von β_2-Mikroglobulin im Plasma durch eine geringe Beeinträchtigung der Nieren verursacht, die vor einem Anstieg von Kreatinin im Serum eintrat. Deshalb ist die Konzentration von β_2-Mikroglobulin im Plasma kein zuverlässiges Anzeichen für die β_2-Mikroglobulinbildung.

2. Die Verwendung der Filtrationsrate von β_2-Mikroglobulin als Hinweis auf eine β_2-Mikroglobulinbildung erlaubte uns, eine Beziehung zwischen β_2-Mikroglobulinbildung und immunologischen Veränderungen (IgG-Konzentration) bei Lebercirrhose nachzuweisen.

Introduction

β_2-Microglobulin is a low molecular weight plasma-protein (M_r = 11800) isolated from the urine of patients with tubular proteinuria by *Berggård* (1). It is a single chain polypeptide synthesized by lymphocytes, mesenchymal and epithelial cells (2, 3). β_2-Microglobulin is eliminated from the blood via glomerular filtration followed by catabolism in the kidneys after tubular reabsorption. Only a small amount of β_2-microglobulin is excreted in the urine. As β_2-microglobulin is freely filtered by glomeruli (4), the product of the β_2-microglobulin plasma level times the glomerular filtration rate (GFR) shows with sufficient accuracy the extent of the filtration rate of β_2-microglobulin.

In the steady state, the filtration rate of β_2-microglobulin can be considered as an indirect index of β_2-microglobulin production, because the extrarenal catabolism of β_2-microglobulin is negligible (5).

Renal function is frequently impaired in liver cirrhosis (6, 7). This can account for an increased β_2-microglobulin plasma level. However, plasma β_2-microglobulin is also often high in cirrhotics without an increased creatinine level (8–11). The pathogenesis of such an increase is not yet clarified. Many authors suppose that it could be consequent on an increased production (8–11). However the creatinine plasma level is not so sensitive an index of the GFR as β_2-microglobulin (12), therefore an increased β_2-microglobulin level in plasma could be due to decreased filtration, even before any of the clinical or biochemical signs of renal failure used in ordinary practice are evident.

The aim of this research was:

a) to study β_2-microglobulin production by means of β_2-microglobulin filtration rate;

b) to compare the β_2-microglobulin plasma level with the β_2-microglobulin production;

c) to investigate the relationships between β_2-microglobulin production and main indices of liver disease; in patients with liver cirrhosis without overt renal failure.

Materials and Methods

The study comprised sixtytwo consecutive in-patients, fortyeight men and fourteen women, suffering from liver cirrhosis, who had not suffered from organic nephropathy and had a creatinine level lower than 13 mg/l. Twentyfour had alcoholic cirrhosis, twenty posthepatitic cirrhosis and eighteen cryptogenic cirrhosis. The mean age of the patients was fortynine years, and the standard deviation was twelve. The diagnosis was made by case history, clinical and laboratory findings and confirmed by histology in thirty cases. In all patients and in sixteen controls (eleven men and five women, mean age forty-five, standard deviation seven) the glomerular filtration rate was measured by means of the inulin clearance. At the same time plasma samples were assayed for aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time, plasma protein electrophoresis and creatinine. The creatinine level was determined by a colorimetric method (Creatinine Test Combination. Cat. No. 124192. Boehringer Mannheim West Germany). Immunoglobulins, measured by a nephelometer, were determined only in the last twentyfour patients studied, because of a planning fault. Ten of them had alcoholic cirrhosis, seven posthepatitic cirrhosis and seven cryptogenic cirrhosis. Immunoglobulin levels in cirrhotics are shown in tab. 1.

Tab. 1. Immunoglobulins in the three groups of cirrhotics.

	IgG (g/l)	IgA (g/l)	IgM (g/l)
Alcoholic cirrhosis	16.58 ± 3.45	5.60 ± 1.06	2.04 ± 1.08
Cryptogenic cirrhosis	20.60 ± 5.64	4.68 ± 2.18	3.16 ± 1.52
Posthepatitic cirrhosis	16.20 ± 4.80	4.36 ± 1.67	2.74 ± 1.59

Range of reference:
IgG 8–18 g/l, IgA 0.6–4.0 g/l, IgM 0.5–2.5 g/l

β_2-Microglobulin was measured in plasma samples obtained during inulin clearance by means of a radioimmunoassay technique (Phadebas Beta-2-micro-test. Pharmacia Diagnostics. Uppsala, Sweden).

Statistics

The normal range for β_2-microglobulin plasma level and β_2-microglobulin filtration rate was considered to be the mean in the controls ±2 s.d. The comparison between the values of the indices of liver damage in patients with normal and high β_2-microglobulin plasma level or β_2-microglobulin filtration rate was carried out with *Student*'s "t" unpaired test; 2 P values in "Table Scientifiques", Geigy 1963, were used to ascertain statistical significance. The significance in the frequency distribution of cirrhotics with high β_2-microglobulin plasma level or β_2-microglobulin filtration rate in the three aetiologic groups was ascertained by the χ^2 method. Linear regression was calculated by the minimal square method. Data are expressed as mean ± standard deviation.

Results

The mean β_2-microglobulin plasma level and mean β_2-microglobulin filtration rate were respectively 1.5 ± 0.6 mg/l and 186 ± 73 µg/min in controls. They were respectively 2.6 ± 1.1 mg/l and 251 ± 122 µg/min in cirrhotic patients. β_2-Microglobulin plasma levels were high in twentysix patients. The β_2-microglobulin filtration rate was high in fourteen; in twelve cases both β_2-microglobulin plasma level and β_2-microglobulin filtration rate were high (fig. 1). The increase in β_2-microglobulin plasma level or β_2-microglobulin filtration rate was not related to the aetiology of cirrhosis (respectively $\chi^2 = 0.32$ and $\chi^2 = 1.1$, not significant). In patients in whom both β_2-microglobulin plasma level and β_2-microglobulin filtration rate were found to be increased, the mean glomerular filtration rate and serum creatinine were respectively 115 ± 31 ml/min and 10 ± 9 mg/l; whereas in patients who had only a high β_2-microglobulin plasma level they were respectively 70 ± 28 ml/min and 11 ± 4 mg/l. Such a difference was highly significant ($t = 4.02$; $p < 0.001$) for the glomerular filtration rate, but not as far as the serum creatinine was concerned ($t = 0.072$). The values of the indices of liver disease were similar in patients with a high β_2-microglobulin plasma level and in those with a low one (tab. 2), whereas the cirrhotics with a high β_2-microglobulin filtration rate showed an increased level of IgG compared with those with a low β_2-microglobulin filtration rate (tab. 3). No correlation was found between β_2-microglobulin plasma level and immunoglobulins. A linear correlation was detected between the β_2-microglobulin filtration rate and IgG (fig. 2).

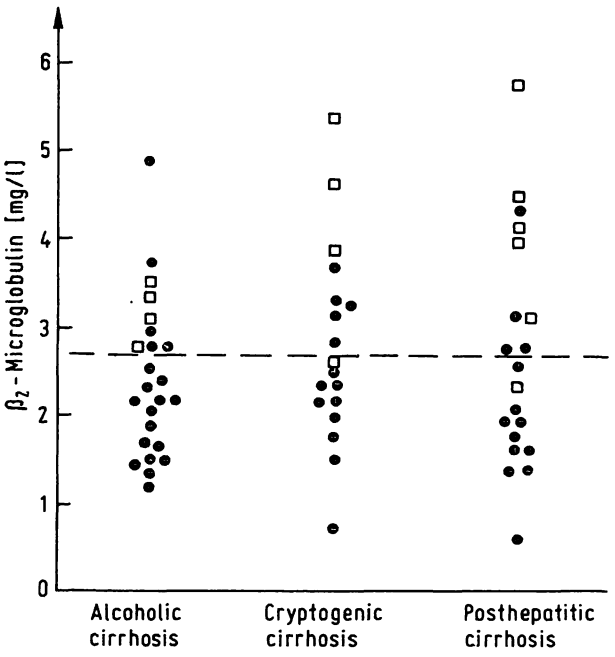

Fig. 1. Concentrations of β_2-microglobulin in plasma in the three groups of cirrhotics (cirrhotics with β_2-microglobulin filtration rate ● within, □ above the normal range; – – – upper limit of the normal range for β_2-microglobulin plasma level).

Tab. 2. Indices of liver disease in patients with or without high β_2-microglobulin plasma level.

Index	High β_2-microglobulin plasma level	Low β_2-microglobulin plasma level	t	P
Aspartate aminotransferase	60 ± 44 U/l	72 ± 58 U/l	0.877	n.s.
Alanine aminotransferase	53 ± 41 U/l	59 ± 71 U/l	0.383	n.s.
Prothrombin time	76 ± 18 %	69 ± 18 %	1.467	n.s.
Total bilirubin	19 ± 13 mg/l	23 ± 25 mg/l	0.770	n.s.
Albumin	33 ± 5 g/l	32 ± 6 g/l	0.696	n.s.
γ-Globulins	21 ± 7 g/l	21 ± 6 g/l	0.000	n.s.
IgG	17.57 ± 5.18 g/l	17.72 ± 4.61 g/l	0.067	n.s.
IgA	4.67 ± 1.98 g/l	5.09 ± 1.54 g/l	0.567	n.s.
IgM	2.09 ± 1.12 g/l	2.67 ± 1.41 g/l	0.881	n.s.

Tab. 3. Indices of liver disease in patients with or without high β_2-microglobulin filtration rate.

Index	High β_2-microglobulin filtration rate	Low β_2-microglobulin filtration rate	t	P
Aspartate aminotransferase	46 ± 39 U/l	71 ± 53 U/l	1.582	n.s.
Alanine aminotransferase	50 ± 63 U/l	59 ± 63 U/l	0.478	n.s.
Prothrombin time	71 ± 17 %	72 ± 19 %	0.165	n.s.
Total bilirubin	21 ± 15 mg/l	22 ± 23 mg/l	0.153	n.s.
Albumin	35 ± 4 g/l	32 ± 6 g/l	1.700	n.s.
γ-Globulins	22 ± 6 g/l	21 ± 7 g/l	0.702	n.s.
IgG	23.30 ± 3.34 g/l	16.75 ± 3.77 g/l	2.818	<0.02
IgA	6.01 ± 1.31 g/l	4.80 ± 1.70 g/l	1.173	n.s.
IgM	2.83 ± 1.07 g/l	2.59 ± 1.65 g/l	0.199	n.s.

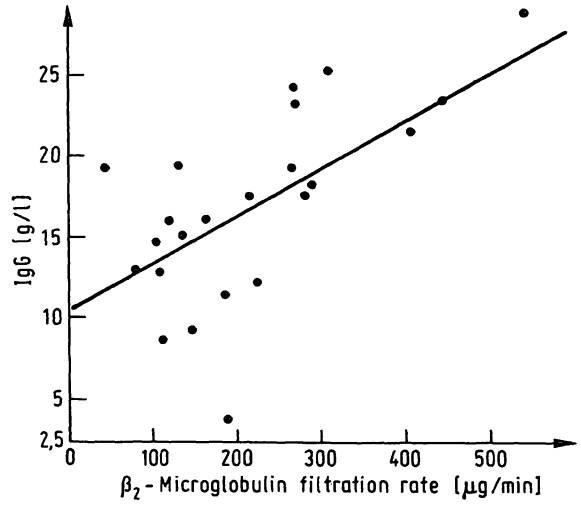

Fig. 2. Correlation between β_2-microglobulin filtration rate (index of β_2-microglobulin production) and IgG: $y = 2.5x + 1173$ ($r = 0.52$ $p < 0.02$).

Discussion

β_2-Microglobulin plasma levels in controls corresponded to those found in the literature (4, 9). The β_2-microglobulin filtration rate corresponded to the production of β_2-microglobulin measured by the disappearance of ^{125}I-labelled β_2-microglobulin from the vascular compartment (4). This is a confirmation of the renal catabolism of β_2-microglobulin and of the value of the β_2-microglobulin filtration rate as an indirect index of β_2-microglobulin production.

A definite rise in β_2-microglobulin production, as shown by an increased β_2-microglobulin filtration rate, was ascertained in 46% of the patients with high β_2-microglobulin plasma levels. In the patients with high β_2-microglobulin plasma levels without an increased β_2-microglobulin filtration rate, the GFR was decreased, but so slightly that on an avarage it did not affect the serum creatinine level. Possibly the reduction in muscle mass, commonly found in cirrhosis, could explain the low sensitivity of serum creatinine as an index of renal function. In fact, serum creatinine depends not only on the GFR, but also on the muscle production of creatinine. Therefore, even if serum creatinine is in the normal range, the high β_2-microglobulin plasma level can often be consequent on a reduction in glomerular filtration, especially in patients with liver cirrhosis, where a decreased renal function is very common (6, 7).

As far as the pathogenesis of the raised production of β_2-microglobulin in liver cirrhosis is concerned, three mechanisms were hypothesized: one, an increased protein release due to hepatic tissue necrosis; two, an increased hepatic synthesis during reparative growth; three, an increased lymphocytic synthesis reflecting an elevated inflammatory activity (8).

In our series, neither the β_2-microglobulin plasma level nor the β_2-microglobulin filtration rate were found to be related to the plasma level of transaminases or to the main indices of liver damage, in agreement with the findings of *Beorchia* (9). Therefore it is unlikely that tissue necrosis and liver function could have any role in the increased production of β_2-microglobulin. Our results do not allow us to express any opinion about an increase in β_2-microglobulin hepatic synthesis (an hypothesis not yet completely elucidated by any author).

The immunological hypothesis is based on the fact that β_2-microglobulin shares many structural features with the immunoglobulin polypeptide chains, particularly with the C_{H3} domain of IgG_1 (2, 14), and it is closely associated with the major human histocompatibility antigens (15, 16); moreover the β_2-microglobulin plasma level in liver diseases decreases during immunosuppressive treatment (9). The linear correlation between the β_2-microglobulin filtration rate and IgG that we found is good evidence in support of this hypothesis. It could be hypothesized that β_2-microglobulin overproduction was an expression of B lymphocyte hyperreactivity due to endotoxin – a potent B cell mitogen – or of the cellular immunity depression found in many chronic liver diseases (17, 18).

A wide variability in the immunologic-phlogistic reactions in the three aetiologic groups of our series could explain why neither β_2-microglobulin plasma level nor β_2-microglobulin filtration rate appeared related to the aetiology of liver cirrhosis.

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